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APPLICATION NUMBER: *60/505,390*
FILING DATE: *September 23, 2003*

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PTO/SB/16 (5-03)
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PROVISIONAL APPLICATION FOR PATENT COVER SHEET

This is a request for filing a PROVISIONAL APPLICATION FOR PATENT under 37 CFR 1.53(c).

INVENTOR(S)		
Given Name (first and middle [if any])	Family Name or Surname	Residence (City and either State or Foreign Country)
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☒ *Additional inventors are being named on the* 1 *separately numbered sheets attached hereto*

09/17 U.S.PTO 60/505390 092303

TITLE OF THE INVENTION (280 characters max)

PHARMACEUTICAL FORMULATIONS

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ENCLOSED APPLICATION PARTS *(check all that apply)*

☒ Specification *Number of Pages*	23	☐ CD(s), Number	
☐ Drawing(s) *Number of Sheets*		☐ Other (specify)	
☐ Application Data Sheet. See 37 CFR 1.76			

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Respectfully submitted,

SIGNATURE

TYPED or PRINTED NAME James P. Riek

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Date 23Sept03

REGISTRATION NO. *(if appropriate)* 39,009

Docket Number: PB60383P1

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Additional Page

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Docket Number	PB60383P1	Type a plus sign (+) inside this box →	+

INVENTOR(S)/APPLICANT(S)		
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Invention:

PHARMACEUTICAL FORMULATIONS

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PHARMACEUTICAL FORMULATIONS

The present invention relates to solid pharmaceutical formulations which comprise an active ingredient drug substance, a carrier and a compound which inhibits or reduces chemical reaction or degradation of the active ingredient substance in the presence of the carrier. The invention also relates to the use of a compound which inhibits or reduces chemical reaction or degradation of an active ingredient substance for the stabilisation of the active ingredient drug substance in the presence of a carrier.

An important requirement of pharmaceutical formulations is that they should be stable on storage in a range of different conditions. It is known that active ingredient substances can demonstrate instability to one or more of heat, light or moisture and various precautions must be taken in formulating and storing such substances to ensure that the pharmaceutical products remain in an acceptable condition for use over a reasonable period of time, such that they have an adequate shelf-life. Instability of a drug substance may also arise from contact with one or more other components present in a formulation, for example a component present as an excipient.

It is usual practice in the pharmaceutical art to formulate active ingredient substance with substances known as excipients which may be required as carriers, diluents, fillers, bulking agents, binders etc. Such excipients are often used to give bulk to a pharmaceutical formulation where the active ingredient substance is present in very small quantities. Such substances are generally chemically inert. Over prolonged storage times, or under conditions of extreme heat or humidity, and in the presence of other materials, such inert substances can, however, undergo or participate in chemical degradation reactions.

Carrier substances that are commonly utilised in solid pharmaceutical formulations include reducing sugars, for example lactose, maltose and glucose. Lactose is particularly commonly used. It is generally regarded as an inert excipient.

However, it has been observed that certain active ingredient substances may undergo a chemical reaction in the presence of lactose and other reducing sugars. For example, it was reported by Wirth *et al.* (*J. Pharm. Sci.*, 1998, **87**, 31-39) that fluoxetine hydrochloride (sold under the tradename Prozac®) undergoes degradation when present in solid tablets

with a lactose excipient. The degradation was postulated to occur by formation of adducts via the Maillard reaction and a number of early Maillard reaction intermediates were identified. The authors conclude that drug substances which are secondary or primary amines undergo the Maillard reaction with lactose under pharmaceutically relevant conditions.

The present inventors have found that, under accelerated stability conditions, certain inhalable active ingredient substances also undergo degradation in the presence of lactose, possibly also via the Maillard reaction.

Some inhalable dry powder pharmaceuticals are sensitive to moisture, as reported, for example in WO 00/28979 (SkyePharma AG). The presence of moisture was found to interfere with the physical interaction between a carrier and a drug substance and thus with the effectiveness of drug delivery. Such interference with physical interactions between a carrier and a drug substance is distinct from chemical instability resulting from degradation.

A further commonly used excipient in solid pharmaceutical formulations is magnesium stearate, which is often included as a lubricant. WO00/28979 (SkyePharma AG) describes the use of magnesium stearate in dry powder formulations for inhalation to improve resistance to moisture and to reduce the effect of penetrating moisture on the fine particle fraction (FPF) of an inhaled formulation. WO00/53158 (Chiesi) describes a powder for use in a dry powder inhaler including an active ingredient and a carrier, wherein the carrier includes a lubricant, which may, for example, be magnesium stearate.

We have now surprisingly found that chemical interaction of active ingredient substance and carrier may be inhibited or reduced by the presence of a ternary agent selected from the groups described below.

In a first aspect therefore the present invention provides the use of a ternary agent to inhibit or reduce chemical interaction between an active ingredient substance and a carrier in a solid pharmaceutical formulation, wherein the active ingredient substance is susceptible to chemical interaction with the carrier and the ternary agent is selected from the group consisting of basic salts and salts of fatty acids.

The invention also provides the use of a ternary agent to inhibit or reduce chemical degradation of an active ingredient substance in a solid pharmaceutical formulation comprising the active ingredient substance and a carrier, wherein said active ingredient substance is susceptible to chemical interaction with said carrier and the ternary agent is selected from the group consisting of basic salts and salts of fatty acids. The chemical stability of the active substance in the formulation during long term storage is thereby improved.

In a second aspect the present invention provides a solid pharmaceutical formulation comprising (a) an active ingredient substance susceptible to chemical interaction with a carrier, (b) a carrier and (c) a ternary agent selected from the group consisting of basic salts and salts of fatty acids.

In a third aspect the present invention provides a method of reducing or inhibiting chemical interaction between an active ingredient substance and a carrier susceptible to chemical interaction, which comprises mixing with said active ingredient substance and said carrier a ternary agent selected from the group consisting of basic salts and salts of fatty acids. The invention also provides a method of inhibiting chemical degradation of an active ingredient substance in a formulation comprising a carrier and an active ingredient substance, which method comprises mixing with said active ingredient substance and said carrier a ternary agent and the ternary agent selected from the group consisting of basic salts and salts of fatty acids.

Pharmaceutical formulations according to the present invention have greater chemical stability than the corresponding formulations without said ternary agent.

'Ternary agent' is used herein to mean a compound used in a formulation in addition to the active ingredient drug substance or substances (the 'primary' agent) and a bulk carrier material or materials (the 'secondary' agent). In some circumstances more than one ternary agent may be used. Optionally, further substances, possibly named 'quaternary agents', may also be present, for example as a lubricant. Any particular ternary or quaternary agent may have more than one effect.

In the present invention. the ternary agent is capable of reducing or inhibiting interaction between a carrier and an active ingredient in a solid pharmaceutical formulation.

Preferred embodiments of ternary agents are as follows: Preferred basic salts include stearates, citrates and hydrogenphosphates. Amongst stearates, there are preferred calcium stearate and magnesium stearate, especially magnesium stearate. Preferred citrates include sodium citrate dihydrate; preferred hydrogen phosphates include sodium hydrogen phosphate. Amongst salts of fatty acids, there are preferred salts of stearates, especially magnesium and calcium stearate.

The invention finds particular application in formulations in which the carrier is a reducing sugar, for example lactose, maltose or glucose (for example monohydrate glucose or anhydrate glucose). In a preferred embodiment, the carrier is lactose. Alternative carriers include maltodextrin.

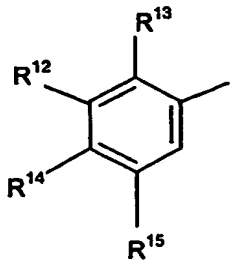
The optimal amount of ternary agent present in a particular composition varies depending on the identity of the ternary agent, the identity of the active ingredient drug substance present, the sizes of the particles and various other factors. In general, the ternary agent is preferably present in an amount of from 0.1 to 20% w/w based on the total weight of the composition. More preferably the ternary agent is present in an amount of from 0.2 to 10% w/w based on the total weight of the composition.

When magnesium stearate is used as the ternary agent, it is preferably present in an amount of from 0.3 to 6% w/w, for example from 0.5 to 4% w/w. When sodium citrate dihydrate is used as the ternary agent, it is preferably present in an amount of from 1 to 8% w/w, for example from 3 to 5% w/w. When sodium hydrogen phosphate is used as the ternary agent, it is preferably present in an amount of from 1 to 8% w/w, for example from 3 to 5% w/w. If more than one different ternary agents are used, the optimal amount of each agent may be proportionally lower than the amounts stated here.

The active ingredient substance is typically present in an amount of from 0.01% to 50% w/w based on the total weight of the composition. Preferably, the active ingredient substance is present in an amount of from 0.02% to 10% w/w, more preferably in an amount of from 0.03 to 5%w/w, for example from 0.05% to 1% w/w, for example 0.1% w/w.

Preferably, the active ingredient drug substance is one which includes the group Ar-CH(OH)-CH_2-NH-R.

Preferably, the group Ar is selected from



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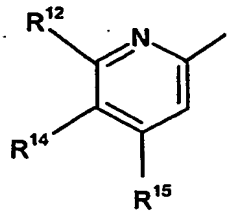

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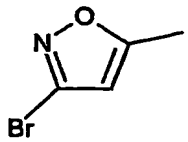
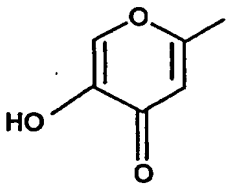


(c)

and



(d)

wherein R^{12} represents halogen, $-(CH_2)_qOR^{16}$, $-NR^{16}C(O)R^{17}$, $-NR^{16}SO_2R^{17}$, $-SO_2NR^{16}R^{17}$, $-NR^{16}R^{17}$, $-OC(O)R^{18}$ or $OC(O)NR^{16}R^{17}$,
and R^{13} represents hydrogen, halogen or C_{1-4} alkyl;

or R^{12} represents $-NHR^{19}$ and R^{13} and $-NHR^{19}$ together form a 5- or 6- membered heterocyclic ring;

R^{14} represents hydrogen, halogen, $-OR^{16}$ or $-NR^{16}R^{17}$;

R^{15} represents hydrogen, halogen, haloC_{1-4} alkyl, $-OR^{16}$, $-NR^{16}R^{17}$, $-OC(O)R^{18}$ or $OC(O)NR^{16}R^{17}$;

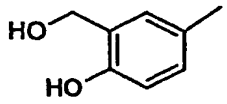
R^{16} and R^{17} each independently represents hydrogen or C_{1-4} alkyl, or in the groups $-NR^{16}R^{17}$, $-SO_2NR^{16}R^{17}$ and $-OC(O)NR^{16}R^{17}$, R^{16} and R^{17} independently represent hydrogen or C_{1-4} alkyl or together with the nitrogen atom to which they are attached form a 5-, 6- or 7- membered nitrogen-containing ring,

R^{18} represents an aryl (eg phenyl or naphthyl) group which may be unsubstituted or substituted by one or more substituents selected from halogen, C_{1-4} alkyl, hydroxy, C_{1-4} alkoxy or halo C_{1-4} alkyl; and

q is zero or an integer from 1 to 4;

A physiologically functional derivative of a drug substance, for example of one of the above-mentioned compounds, may also be used in the invention. By the term "physiologically functional derivative" is meant a chemical derivative of a compound of having the same physiological function as the free compound, for example, by being convertible in the body thereto. According to the present invention, examples of physiologically functional derivatives include esters, for example compounds in which a hydroxyl group has been converted to a C_{1-6}alkyl, aryl, aryl C_{1-6} alkyl, or amino acid ester.

Within the definitions of (a) and (b) above, preferred groups may be selected from the following groups (i) to (xxi):



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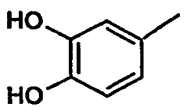

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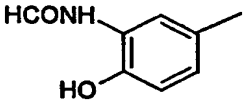

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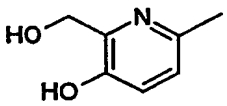

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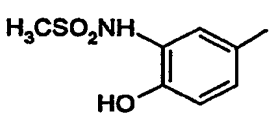

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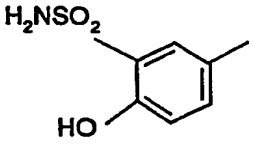

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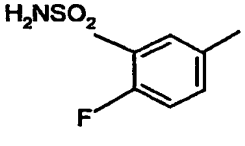

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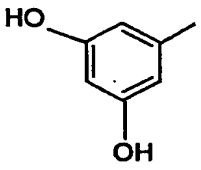

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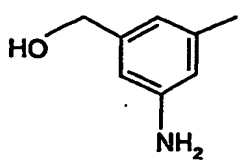

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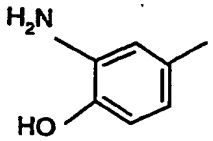

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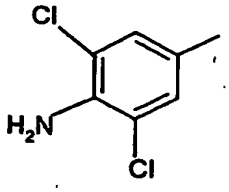

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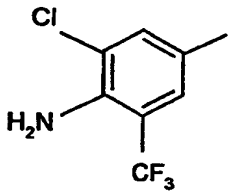

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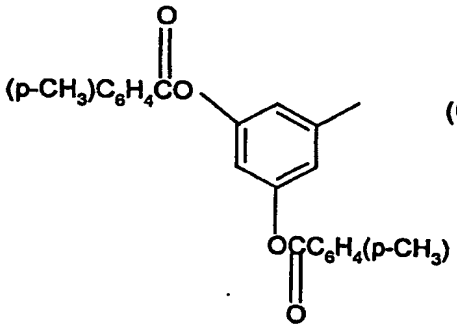

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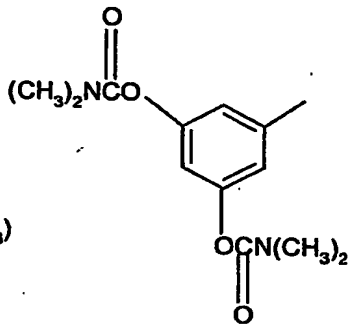

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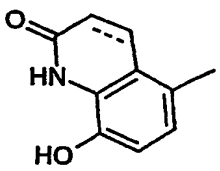

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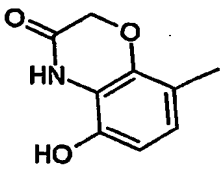

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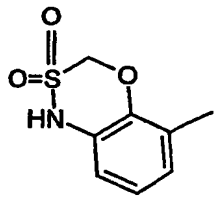

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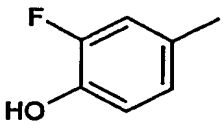

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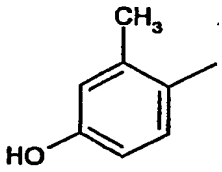

(xxi)

wherein the dotted line in (xvi) and (xix) denotes an optional double bond.

The group R preferably represents a moiety of formula:

-A-B-C-D

Wherein

A may represent $(CH_2)_m$ wherein m is an integer from 1 to 10;

B may represent a heteroatom, e.g. oxygen;

C may represent $(CH_2)_n$ wherein n is an integer from 1 to 10; and

D may represent an aryl group, e.g. an optionally substituted phenyl or pyridyl group.

The active ingredient drug substance may be present as a salt or a solvate. Salts and solvates which are suitable for use in medicine are those wherein the counterion or associated solvent is pharmaceutically acceptable.

Suitable salts for use in the invention include those formed with both organic and inorganic acids or bases. Pharmaceutically acceptable acid addition salts include those formed from hydrochloric, hydrobromic, sulphuric, citric, tartaric, phosphoric, lactic, pyruvic, acetic, trifluoroacetic, triphenylacetic, phenylacetic, substituted phenyl acetic eg. methoxyphenyl acetic, sulphamic, sulphanilic, succinic, oxalic, fumaric, maleic, malic, glutamic, aspartic, oxaloacetic, methanesulphonic, ethanesulphonic, arylsulponic (for example p-toluenesulphonic, benzenesulphonic, naphthalenesulphonic or naphthalenedisulphonic), salicylic, glutaric, gluconic, tricarballylic, mandelic, cinnamic, substituted cinnamic (for example, methyl, methoxy, halo or phenyl substituted cinnamic, including 4-methyl and 4-methoxycinnamic acid and α-phenyl cinnamic acid (E or Z isomers or a mixture of the two)), ascorbic, oleic, naphthoic, hydroxynaphthoic (for example 1- or 3-hydroxy-2-naphthoic), naphthaleneacrylic (for example naphthalene-2-acrylic), benzoic, 4-methoxybenzoic, 2- or 4-hydroxybenzoic, 4-chlorobenzoic, 4-phenylbenzoic, bezeneacrylic (for example 1,4-benzenediacrylic) and isethionic acids. Pharmaceutically acceptable base salts include ammonium salts, alkali metal salts such as those of sodium and potassium, alkaline earth metal salts such as those of calcium and magnesium and salts with organic bases such as dicyclohexyl amine and N-methyl-D-glucamine.

The active ingredient drug substance is most preferably a selective long-acting β_2-adrenoreceptor agonist. Such compounds have use in the prophylaxis and treatment of a variety of clinical conditions, including diseases associated with reversible airways obstruction such as asthma, chronic obstructive pulmonary diseases (COPD) (e.g. chronic and wheezy bronchitis, emphysema), respiratory tract infection and upper respiratory tract disease (e.g. rhinitis, including seasonal and allergic rhinitis).

Other conditions which may be treated include premature labour, depression, congestive heart failure, skin diseases (e.g. inflammatory, allergic, psoriatic, and proliferative skin diseases), conditions where lowering peptic acidity is desirable (e.g. peptic and gastric ulceration) and muscle wasting disease.

Preferred active drug substances for use in the present invention include those described in WO 02/066422, WO 02/070490, WO 02/076933, WO 03/024439, PCT/EP03/02301 and PCT/EP03/04367, the contents of which are incorporated herein by reference as though set out in full herein. For example the drug substance may be 3-(4-{[6-({(2R)-2-hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl}amino) hexyl]oxy}-butyl)benzene-sulfonamide, for example as its cinnamate salt.

Formulations to which the present invention may be applied include those suitable for oral, parenteral (including subcutaneous, intradermal, intramuscular, intravenous and intraarticular), inhalation (including fine particle dusts or mists which may be generated by means of various types of metered dose pressurised aerosols, nebulisers or insufflators), rectal and topical (including dermal, buccal, sublingual and intraocular) administration although the most suitable route may depend upon for example the condition and disorder of the recipient. The formulations may conveniently be presented in unit dosage form and may be prepared by any of the methods well known in the art of pharmacy. All methods include the step of bringing the active ingredient into association with the carrier and the ternary agent as well as any other accessory ingredients. In general the formulations are prepared by uniformly and intimately bringing into association the active ingredient, lactose, ternary agent and any other accessory ingredients, and then, if necessary, shaping the product into the desired formulation.

Formulations of the present invention suitable for oral administration may be presented as discrete units such as capsules, cachets or tablets each containing a predetermined

amount of the active ingredient; as a powder or granules. The active ingredient drug substance may also be presented as a bolus, electuary or paste.

A tablet may be made by compression or moulding, optionally with one or more accessory ingredients. Compressed tablets may be prepared by compressing in a suitable machine the active ingredient in a free-flowing form such as a powder or granules, optionally mixed with a binder, lubricant, inert diluent, lubricating, surface active or dispersing agent. Moulded tablets may be made by moulding in a suitable machine a mixture of the powdered compound moistened with an inert liquid diluent. The tablets may optionally be coated or scored and may be formulated so as to provide slow or controlled release of the active ingredient therein.

Formulations for parenteral administration include sterile powders, granules and tablets intended for dissolution immediately prior to administration. The formulations may be presented in unit-dose or multi-dose containers, for example sealed ampoules and vials, and may be stored in a freeze-dried (lyophilised) condition requiring only the addition of the sterile liquid carrier, for example saline or water-for-injection, immediately prior to use.

Formulations for rectal administration may be presented as a suppository with the usual carriers such as cocoa butter or polyethylene glycol.

Formulations for topical administration in the mouth, for example buccally or sublingually, include lozenges comprising the active ingredient in a flavoured basis such as sucrose and acacia or tragacanth, and pastilles comprising the active ingredient in a basis such as gelatin and glycerin or sucrose an acacia.

The invention finds particular application in dry powder compositions for topical delivery to the lung by inhalation.

Dry powder compositions for topical delivery to the lung by inhalation may, for example, be presented in capsules and cartridges of for example gelatine, or blisters of for example laminated aluminium foil, for use in an inhaler or insufflator. Packaging of the formulation may be suitable for unit dose or multi-dose delivery. In the case of multi-dose delivery, the formulation can be pre-metered (eg as in Diskus, see GB 2242134 or Diskhaler, see GB 2178965, 2129691 and 2169265) or metered in use (eg as in Turbuhaler, see EP 69715). An example of a unit-dose device is Rotahaler (see GB 2064336). The Diskus inhalation

device comprises an elongate strip formed from a base sheet having a plurality of recesses spaced along its length and a lid sheet hermetically but peelably sealed thereto to define a plurality of containers, each container having therein an inhalable formulation containing an active compound. Preferably, the strip is sufficiently flexible to be wound into a roll.

Medicaments for administration by inhalation desirably have a controlled particle size. The optimum particle size for inhalation into the bronchial system is usually 1-10μm, preferably 2-5μm. Particles having a size above 20μm are generally too large when inhaled to reach the small airways. To achieve these particle sizes the particles of the active ingredient substance as produced may be size reduced by conventional means eg by micronisation. The desired fraction may be separated out by air classification or sieving. Preferably, the particles will be crystalline. In general, the particle size of the carrier, for example lactose, will be much greater than the drug substance within the present invention. It may also be desirable for other agents other than the active drug substance to have a larger particle size than the active drug substance. When the carrier is lactose it will typically be present as milled lactose, for example with a MMD of 60-90μm and with not more than 15% having a particle diameter of less than 15μm.

Preferred unit dosage formulations are those containing an effective dose, as hereinbefore recited, or an appropriate fraction thereof, of the active ingredient.

It should be understood that in addition to the ingredients particularly mentioned above, the formulations of this invention may include other agents conventional in the art having regard to the type of formulation in question, for example those suitable for oral administration may include flavouring agents.

The compounds and pharmaceutical formulations according to the invention may be used in combination with or include one or more other therapeutic agents, for example a beta-agonist may be used in combination with one or more other therapeutic agents selected from anti-inflammatory agents (for example a corticosteroid, or an NSAID,) anticholinergic agents (particularly an M_1, M_2, M_1/M_2 or M_3 receptor antagonist), other β_2-adrenoreceptor agonists, antiinfective agents (e.g. antibiotics, antivirals), or antihistamines.

Suitable corticosteroids include methyl prednisolone, prednisolone, dexamethasone, fluticasone propionate, 6α,9α-difluoro-17α-[(2-furanylcarbonyl)oxy]-11β-hydroxy-16α-methyl-3-oxo-androsta-1,4-diene-17β-carbothioic acid *S*-fluoromethyl ester, 6α,9α-difluoro-11β-hydroxy-16α-methyl-3-oxo-17α-propionyloxy- androsta-1,4-diene-17β-carbothioic acid *S*-(2-oxo-tetrahydro-furan-3S-yl) ester, beclomethasone esters (e.g. the 17-propionate ester or the 17,21-dipropionate ester), budesonide, flunisolide, mometasone esters (e.g. the furoate ester), triamcinolone acetonide, rofleponide, ciclesonide, butixocort propionate, RPR-106541, and ST-126.

Suitable NSAIDs include sodium cromoglycate, nedocromil sodium, phosphodiesterase (PDE) inhibitors (e.g. theophylline, PDE4 inhibitors or mixed PDE3/PDE4 inhibitors), leukotriene antagonists, inhibitors of leukotriene synthesis, iNOS inhibitors, tryptase and elastase inhibitors, beta-2 integrin antagonists and adenosine receptor agonists or antagonists (e.g. adenosine 2a agonists), cytokine antagonists (e.g. chemokine antagonists) or inhibitors of cytokine synthesis.

Suitable anticholinergic agents are those compounds that act as antagonists at the muscarinic receptor, in particular those compounds which are antagonists of the M_1 and M_2 receptors. Exemplary compounds include the alkaloids of the belladonna plants as illustrated by the likes of atropine, scopolamine, homatropine, hyoscyamine; these compounds are normally administered as a salt, being tertiary amines.

Preferred anticholinergics include ipratropium (e.g. as the bromide), sold under the name Atrovent, oxitropium (e.g. as the bromide) and tiotropium (e.g. as the bromide) (CAS-139404-48-1).

Suitable antihistamines (also referred to as H_1-receptor antagonists) include any one or more of the numerous antagonists known which inhibit H_1-receptors, and are safe for human use. All are reversible, competitive inhibitors of the interaction of histamine with H_1-receptors. Examples of preferred anti-histamines include methapyrilene and loratadine.

The invention further provides the use of an inhalable solid pharmaceutical formulation according to the invention for the manufacture of a medicament for the treatment of diseases associated with reversible airways obstruction such as asthma, chronic obstructive pulmonary diseases (COPD) (e.g. chronic and wheezy bronchitis,

emphysema), respiratory tract infection and upper respiratory tract disease (e.g. rhinitis, including seasonal and allergic rhinitis). The invention also provides a method fortreating asthma, chronic obstructive pulmonary diseases (COPD), chronic or wheezy bronchitis, emphysema, respiratory tract infection upper respiratory tract, or rhinitis, including seasonal and allergic rhinitiscomprising administering to a patient in need thereof an inhalable solid pharmaceutical formulation according to the invention.

In a further aspect, the invention provides a method of preparing a solid pharmaceutical preparation comprising combining in one or more steps: (a) an active ingredient substance susceptible to interaction with a carrier, (b) a carrier and (c) a ternary agent selected from the group consisting of basic salts and salts of fatty acids.

Examples

Test compound

In the following examples, the drug compound, "Compound X" was the cinnamate salt of 3-(4-{[6-({(2R)-2-hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl}amino)hexyl]oxy}-butyl)benzene-sulfonamide. The synthesis of compound X is described in Examples 45 and 46 in WO 02/066422.

Method

Preparation of blends

Lactose monohydrate was obtained from Borculo Domo Ingredients as BP/USNF form. Before use, the Lactose Monohydrate was sieved through a coarse screen (mesh size 500 microns). Compound X was micronised before use in an APTM microniser to give a MMD (mean mass diameter) of from 2 to 5 microns.

Magnesium stearate was obtained from Peter Greven with MMD < 10 microns and used as supplied. Sodium citrate dihydrate was obtained from Sigma Aldrich and it was ground with a mortar and pestle before use. Sodium hydrogenphosphate was obtained from Sigma Aldrich and it was ground with a mortar and pestle before use.

The ternary agent was combined with lactose monohydrate and blended using either a high shear mixer (a QMM, PMA or TRV series mixer) or a low shear tumbling blender (a Turbula mixer) to provide a ternary agent/drug premix, hereinafter referred to as blend A.

Final blend B was obtained by first pre-mixing an appropriate quantity of blend A with compound X and then blending that blend A/compound X premix with further blend A in a weight ratio appropriate to provide blend B containing the ternary agent in the required quantity, as indicated in Table 1 and Tables 2 to 4 below. The quantity of ternary agent in the Tables 2 to 4 is the amount by weight of ternary agent present as a percentage of the total composition. The final concentration of compound X in the blends was 0.1% w/w calculated on the basis of the weight of free base drug present.

For use in example 2, the blended composition was transferred into blister strips or the type generally used for the supply of dry powder for inhalation and the blister strips were sealed in the customary fashion.

The quantity of the various materials used in the various blends are shown in Table 1:

Table 1:

Excipient	Mass of excipient	Mass of compound X	Mass of lactose
None	-	0.14g	99.86g
2% Mg stearate	2.00g	0.14g	97.86g
1% Mg stearate	1.00g	0.14g	98.86g
0.5% Mg stearate	0.50g	0.14g	99.36g
4% Sodium citrate dihydrate	4.00g	0.14g	95.86g
4% Sodium hydrogen phosphate	4.00g	0.14g	95.86g

0.14g of compound X in the form of the cinnamate salt was used to provide 0.1g of compound X free base.

Decomposition conditions

The blends prepared as described above were subjected to accelerated decomposition conditions in a controlled atmosphere stability cabinet. In the tables below, the conditions to which the blends were subjected are given with reference to the temperature and the %

relative humidity, for example 30/60 is 30°C and 60% relative humidity. Samples were analysed for decomposition products after the time periods indicated in the tables.

Analysis f purity of blends after subjection to decomposition conditions

LC analysis was conducted on a Supelcosil ABZ+PLUS column (150 x 4.6mm ID), 3 micron, eluting with water containing 0.05% trifluoroacetic acid (solvent A) and acetonitrile containing 0.05% v/v trifluroacetic acid (solvent B), using the following elution gradient: time 0 = 90% solvent A, 10% solvent B; 40 mins = 10% solvent A, 90% solvent B; 41-45 mins 90% solvent A, 10% solvent B, . Flow rate was 1ml/min and the column temperature was 40°C. Detection was carried out by UV at 220nm with a HP1100 series detector model G1314A-VWD. The area under the LC trace curve for the total impurities was compared with the total area under the curve, to give the %area/area figures given in Tables 2 to 4.

Results

Example 1: Comparison of compound X / lactose blends comprising magnesium stearate with controls

Table 2:

Blend Details	Timepoint	Condition	Total Impurities (% area/area)
Compound X with Lactose only	Week 2	30/60	5.0
		40/75	8.9
	MN6	30/60	12.7
		40/75	17.4
Compound X with Lactose and 2% Magnesium Stearate	Week 2	30/60	3.4
		40/75	5.3
	MN6	30/60	4.1
		40/75	5.1

Example 2: Comparison of compound X / lactose blends comprising 0.5%, 1.0% and 2.0% magnesium stearate filled into blister strips with controls

Table 3:

Blend Details	Timepoint	Condition	Total Impurities (% area/area)
Compound X with Lactose only	Initial	Initial	3.7
	MN1	25/60	3.7
		30/60	4.3
		40/75	6.3
Compound X with Lactose and 0.5% Magnesium Stearate	Initial	Initial	3.2
	MN1	25/60	3.0
		30/60	3.0
		40/75	3.8
Compound X with Lactose and 1.0% Magnesium Stearate	Initial	Initial	3.2
	MN1	25/60	3.2
		30/60	3.3
		40/75	3.8
Compound X with Lactose and 2.0% Magnesium Stearate	Initial	Initial	3.1
	MN1	25/60	3.2
		30/60	3.3
		40/75	3.7

Example 3: Comparison of compound X / lactose blends comprising 4% Sodium Citrate Dihydrate and 4% Sodium Hydrogenphosphate with controls

Table 4:

Blend Details	Timepoint	Condition	Total Impurities (% area/area)
Compound X with Lactose only	Initial	Initial	3.3
	MN1	25/60	4.7
		40/75	12.6
Compound X with Lactose and 4% Sodium Citrate dihydrate	Initial	Initial	3.6
	MN1	25/60	6.2
		40/75	10.0

Compound X with Lactose and 4% Sodium Hydrogenphosphate	Initial	Initial	3.6
	MN1	25/60	7.3
		40/75	7.5

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CLAIMS

1. A method of inhibiting or reducing chemical interaction between an active ingredient substance and a carrier in a solid pharmaceutical formulation, where the active ingredient substance is susceptible to chemical interaction with the carrier, said method comprises the inclusion of a ternary agent in a solid pharmaceutical formulation comprising an active ingredient substance and a carrier, said ternary agent being present in an amount sufficient to inhibit or reduce chemical interaction between said active ingredient substance and said carrier and the ternary agent is selected from the group consisting of basic salts and salts of fatty acids.

2. The method of claim 1 wherein the ternary agent is a basic salt selected from the group consisting of stearates, citrates and hydrogenphosphates.

3. The method of claim 2 wherein the ternary agent is magnesium stearate, sodium citrate dihydrate or sodium hydrogen phosphate.

4. The method of claims 1 wherein the carrier is a reducing sugar.

5. The method of claim 4 wherein the carrier is lactose.

6. The method of claim 1 wherein the ternary agent is present in an amount of from 0.1 to 20% w/w based on the total weight of the composition.

7. The method of claim 1 wherein the active ingredient substance is present in an amount of from 0.01% to 50% w/w based on the total weight of the composition.

8. The method of claim 1 wherein the drug substance is one which includes the group Ar-CH(OH)-CH_2-NH-R.

9. The method of claim 1 wherein the solid pharmaceutical formulation is for administration by inhalation.

10. A method of inhibiting or reducing chemical degradation of an active ingredient substance in a solid pharmaceutical formulation comprising an active ingredient substance and a carrier, wherein said active ingredient substance is susceptible to

chemical interaction with said carrier, said method comprising the inclusion of a ternary agent, in a pharmaceutical formulation comprising an active ingredient agent and a carrier in an amount sufficient to inhibit or reduce chemical interaction between said active ingredient substance and said carrier and said ternary agent comprising a basic salt selected from the group consisting of stearates, citrates and hydrogenphosphates,.

11. Use method of claim 10 wherein the ternary agent is magnesium stearate, sodium citrate dihydrate or sodium hydrogen phosphate.

12. The method of claim 11 wherein the ternary agent is cellobiose octaacetate.

13. The method of claims 10 wherein the carrier is a reducing sugar.

14. The method of claim 13 wherein the carrier is lactose.

15. The method of claim 10 wherein the ternary agent is present in an amount of from 0.1 to 20% w/w based on the total weight of the composition.

16. The method of claim 10 wherein the active ingredient substance is present in an amount of from 0.01% to 50% w/w based on the total weight of the composition.

17. The method of claim 10 wherein the drug substance is one which includes the group Ar-CH(OH)-CH_2-NH-R.

18. The method of claim 10 wherein the solid pharmaceutical formulation is for administration by inhalation.

19. An inhalable solid pharmaceutical formulation comprising (a) an active ingredient substance susceptible to chemical interaction with lactose, (b) a carrier and (c) a ternary agent capable of reducing or inhibiting chemical interaction between a carrier and an active ingredient substance in a solid pharmaceutical formulation, wherein said ternary agent is selected from the group consisting of basic salts and salts of fatty acids.

20. The inhalable solid pharmaceutical formulation of claim 19 wherein the ternary agent is a basic salt selected from the group consisting of stearates, citrates and hydrogenphosphates.

21. The inhalable solid pharmaceutical formulation of claim 20 wherein the ternary agent is magnesium stearate, sodium citrate dihydrate or sodium hydrogen phosphate.

22. The inhalable solid pharmaceutical formulation of claim 19 wherein the ternary agent is cellobiose octaacetate.

23. The inhalable solid pharmaceutical formulation of claim 19 wherein the carrier is a reducing sugar.

24. The inhalable solid pharmaceutical formulation of claim 19 wherein the carrier is lactose.

25. The inhalable solid pharmaceutical formulation of claim 19 wherein the ternary agent is present in an amount of from 0.1 to 20% w/w based on the total weight of the composition.

26. The inhalable solid pharmaceutical formulation of claim 19 wherein the active ingredient substance is present in an amount of from 0.01% to 50%w/w based on the total weight of the composition.

27. The inhalable solid pharmaceutical formulation of claim 19 wherein the drug substance is one which includes the group Ar-CH(OH)-CH_2-NH-R.

28. The inhalable solid pharmaceutical formulation of claim 19 wherein the solid pharmaceutical formulation is for administration by inhalation.

29. A method of reducing or inhibiting chemical interaction between an active ingredient substance and a carrier susceptible to chemical interaction, which comprises mixing a ternary agent selected from the group consisting of basic salts and salts of fatty acids with said active ingredient substance and said carrier.

30. A method of inhibiting chemical degradation of an active ingredient substance in a formulation comprising a carrier and an active ingredient substance, which method comprises mixing a ternary agent selected from the group consisting of basic salts and salts of fatty acids with said active ingredient substance and said carrier.

31. A method manufacture of a medicament for the treatment of asthma, chronic obstructive pulmonary disease (COPD), chronic or wheezy bronchitis, emphysema, respiratory tract infection, upper respiratory tract disease or rhinitis, including seasonal and allergic rhinitis comprising inclusion of an inhalable solid pharmaceutical formulation as claimed in claim 19 in said medicament.

32. A method for treating asthma, chronic obstructive pulmonary diseases (COPD), chronic or wheezy bronchitis, emphysema, respiratory tract infection, upper respiratory tract disease, or rhinitis, comprising administering to a patient in need thereof an inhalable solid pharmaceutical formulation as claimed in claim 19 in said medicament.

33. A method of preparing a solid pharmaceutical preparation comprising combining in one or more steps: (a) an active ingredient substance susceptible to interaction with a carrier, (b) a carrier and (c) a ternary agent capable of reducing or inhibiting interaction between a carrier and an active ingredient substance, and said ternary agent being selected from the group consisting of basic salts and salts of fatty acids, in a solid pharmaceutical formulation.

34. An inhaler device comprising the inhalable solid pharmaceutical formulation of claim 19.

35. An inhaler device comprising the inhalable solid pharmaceutical formulation of claim 20.

36. An inhaler device comprising the inhalable solid pharmaceutical formulation of claim 21.

37. An inhaler device comprising the inhalable solid pharmaceutical formulation of claim 22.

38. An inhaler device comprising the inhalable solid pharmaceutical formulation of claim 23.

39. An inhaler device comprising the inhalable solid pharmaceutical formulation of claim 24.

40. An inhaler device comprising the inhalable solid pharmaceutical formulation of claim 25.

41. An inhaler device comprising the inhalable solid pharmaceutical formulation of claim 26.

42. An inhaler device comprising the inhalable solid pharmaceutical formulation of claim 27.

43. An inhaler device comprising the inhalable solid pharmaceutical formulation of claim 29.

44. An inhaler device comprising the inhalable solid pharmaceutical formulation of claim 30.

ABSTRACT

The invention relates to the use of a ternary agent to inhibit or reduce chemical interaction between an active ingredient substance and a carrier in a solid pharmaceutical formulation, wherein the active ingredient substance is susceptible to chemical interaction with the carrier and the ternary agent is selected from the group consisting of basic salts and salts of fatty acids. An inhalable solid pharmaceutical formulation comprising (a) an active ingredient substance susceptible to chemical interaction with lactose, (b) a carrier and (c) a ternary agent selected from the group consisting of basic salts and salts of fatty acids is also provided together with uses thereof and methods related thereto.